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## FINAL REPORT

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### Self-Motion Perception and Motion Sickness.

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TO CASE



## TABLE OF CONTENTS

I. INTRODUCTION .....	3
II. PRINCIPLE AREAS of INVESTIGATION .....	3
A. Behavioral Measures .....	3
1. Pica .....	4
2. CTA .....	4
3. Anorexia .....	4
B. Effective Stimulus Parameters .....	5
C. Neuroanatomy and Physiology .....	5
1. Vasopressin .....	5
2. Area Postrema .....	6
3. Vagus Nerve .....	6
4. Immunocytochemistry .....	6
D. Species Differences .....	7
III. CONCLUSIONS	
IV. REFERENCES .....	8
V. LIST OF FIGURES	
Figure 1. Mean Food Intake and Body Weight by Rats Exposed to Off-Vertical Rotation. ....	10
Figure 2. Mean Food Intake and Body Weight by Rats Exposed to Parabolic Flight. ....	11
Figure 3. Mean Fluid Intake by Rats Prior to and Following Exposure to Parabolic Flight. ....	12
VI. APPENDIX I. RESEARCH PAPERS .....	13
V. APPENDIX II. PAPERS PRESENTATED AT SCIENTIFIC MEETINGS .....	15



## I. INTRODUCTION

Motion sickness typically is considered a bothersome artifact of exposure to passive motion in vehicles of conveyance. This condition seldom has significant impact on the health of individuals because it is of brief duration, it usually can be prevented by simply avoiding the eliciting condition and, when the conditions that produce it are unavoidable, sickness dissipates with continued exposure.

However, unavoidable motion sickness is a malady that can have significant effects on the performance of affected individuals. Because the susceptibility of individuals to motion sickness cannot be predicted with precision, some individuals can be seriously affected if they are required to work in an environment that produces motion sickness. The affliction of individuals of unknown susceptibility by this malady can become important when sickness could arise during periods where complicated but necessary performance is demanded. The occurrence of space motion sickness during entry into or return from space flight is one possible case of this type. Important human activities are required during launch and landing of the Space Shuttle, precisely the times when "space sickness" can occur.

There is some debate about the equivalence of motion sickness produced in ground-based studies and "space sickness". However, ground-based studies provide certain benefits over flight studies. Ground-based studies can be conducted at considerable cost savings, the necessary control conditions can be included with experimental rigor, and the appropriate number of subjects can be used to address the experimental questions. Because there are numerous similarities between motion sickness and space sickness, it appears that better knowledge of motion sickness could significantly benefit the understanding and future study of space sickness.

The studies conducted in this research project examined several aspects of motion sickness in animal models. A principle objective of these studies was to investigate the neuroanatomy that is important in motion sickness with the objectives of examining both the utility of putative models and defining neural mechanisms that are important in motion sickness.

## II. PRINCIPLE AREAS of INVESTIGATION

For purposes of exposition, the studies and research findings have been classified into four

categories. These categories are used to organize the presentation of the results and to facilitate the discussion of motion sickness in animal models. Thus, the results of these studies of motion sickness in animal models are organized with the following categories: (a) behavioral measures of the phenomenon, (b) stimuli that are effective for producing the phenomenon, (c) neuroanatomical structures and physiological events that are related to the phenomenon, and (d) differences between species in the elicitation of the phenomenon.

The first two of these categories, behavioral measures and effective stimuli, were addressed in the initial experiments because results from these two categories of studies were fundamental to planning other experiments. After behavioral measures had been subjected to initial validation and appropriate parameters were established for eliciting stimulation, studies were conducted to examine neural structures and physiological events that were related to motion sickness. As studies related to these questions progressed, the issue of species differences in the response began to arise and this was subjected to both retrospective analysis and direct experimental examination.

### A. Behavioral Measures

Frank sickness, or vomiting, is the only universally accepted response that defines motion sickness in all species. None-the-less, many other responses (e.g., pallor, increased salivation, defecation) are commonly considered to be part of the general syndrome of motion sickness. In studies of motion sickness in humans nausea, a measure that is obtained only by self report, commonly is used as a prominent prodromal symptom of sickness.

Nausea and other prodromal symptoms that are detected by self report can be used in humans, but there are no reliable methods for obtaining self reports of symptoms in animals. Because of this, two alternative methods are used to assess the development of motion sickness in animal models. One system is to use rating scales based on the assessment of various responses that are putative prodromal symptoms. Such scales have been developed for use with cats, squirrel monkeys and chimpanzees (Fox, 1992). An extensive discussion of rating scales with animals is presented by Dauntton (1989). The second strategy is to use specific responses (e.g., conditioned taste aversion) that are thought to be related to neural or physiological mechanisms that underlay motion sickness. This strategy has been used with animals that do not have a

complete emetic reflex and as multiple or supplemental indices of sickness (Ossenkopp & Ossenkopp, 1985).

Experimental studies were conducted to evaluate pica, conditioned taste aversion (CTA), and anorexia as putative measures of motion sickness. Pica was proposed as a measure of gastric distress and motion sickness by Mitchell (1977). This response was selected for assessment because it results as increased responding rather than as reduced responding which is common with many of the other putative measures for animal models (Fox, 1990). CTA is the measure most commonly asserted and best documented for assessing nausea and sickness in animals. Anorexia commonly occurs with motion sickness in humans and anecdotally also in animals that have a complete emetic reflex. Consequently this measure was evaluated in several experiments.

### 1. Pica.

Pica was studied in rats with sickness induced by vertical and off-vertical rotation at 150°/s. No reliable pica response was produced by this treatment when appropriate groups were used to control for confounded effects of food deprivation. Pica could be induced by exposing food-deprived animals to motion, but food deprivation itself also induced pica.

This result is in contrast to data reported by Mitchell (1977). It should be noted, however, that studies showing pica in rats have used intense motion stimuli (e.g., 7500°/s) or severe gastric irritants as inducing treatments. The purpose of these preliminary studies in this project was to investigate whether pica could be produced in rats using moderate motion conditions that were representative of treatments known to produce motion sickness in man and other animals. In that regard the answer to the experimental question was that pica was not a useful measure.

### 2. CTA.

It has long been recognized that CTA can be produced by numerous interventions, including motion, that are known to produce gastric distress in humans and animals. This relationship between CTA and "internal malaise" has led to widespread interest in using CTA to assess several forms of sickness arising from gastric disruption in animal models. Several observations have indicated that CTA may be a useful measure of motion sickness in animal models. Important among these is the demonstration that an intact vestibular system is

equally crucial for the production of motion sickness in man and CTA in animals. This, and other relevant relations are reviewed in Fox (1990).

In this project it was demonstrated that CTA is produced by exposure to several forms motion of moderate magnitude that are known to produce vomiting in animals with a complete emetic reflex and in humans (Fox & Daunton, 1982; Fox *et al.*, 1984). However, the precise utility of CTA as a measure of motion sickness remains to be described. A paramount concern in this regard is that the relationship between vomiting and CTA is not isomorphic in either cats or squirrel monkeys (Fox *et al.*, 1990). Because CTA is not precisely related to the universal symptom of motion sickness in species with a complete emetic reflex, the validity of CTA as a prodromal symptom in these species and as a primary index of sickness in rodents that fail to vomit is uncertain.

### 3. Anorexia.

Two experiments were conducted to directly test anorexic and conditioning effects of motion. These effects were assessed by exposing animals to either off-vertical rotation or to parabolic flight using 15 parabolas in a Lear jet. Anorexia was assessed in rats permitted to feed for 2h per day with exposure to motion on test days occurring just prior to the feeding session. CTA was conducted using procedures described elsewhere (Fox & Daunton, 1982).

The mean daily consumption of food in the experiment using off-vertical rotation is shown in Figure 1. Food consumption increased and body weight decreased over the initial days of adaptation to the restricted feeding regimen (2 h/day) until intake stabilized by about Day 11. Using Day 19 (the day preceding exposure to motion) as a baseline, anorexia was present on the day of exposure to motion (on Day 20,  $p < .001$ ) but intake on Days 21 & 22 did not differ from baseline ( $p > .39$ ). Body weight was suppressed on each of the three days following exposure to motion ( $p < .003$ ).

The mean daily consumption of food in the experiment using parabolic flight is shown in Figure 2. Again, food consumption increased as the animals adapted to the restricted feeding schedule (2 h/day) with body weight reflecting an initial decrease (first 5 days) followed by a normal tendency to increase. On Day 12 the rats were transported to the flight line and loaded on the airplane to determine whether this activity would affect the dependent measures. No effects were seen on either food intake or body weight with this procedure ( $F < 1$ ). With Day 18 as a

baseline, anorexia was present immediately after the flight (Day 19) and 48 h later (Day 20). Food consumption 72 h after the flight did not differ from that preceding the flight ( $p>.80$ ). Food intake was suppressed immediately and 24 h following flight ( $ps<.002$ ) but by 48 h after the flight food intake did not differ from the baseline ( $p>.11$ ).

The effects of parabolic flight on CTA are shown in Figure 3. Intake of flavored fluid by animals in the Control and Flight groups did not differ prior to the flight, but in the test following parabolic flight the Control group consumed more fluid than did the animals in the Flight group ( $p<.001$ ). It should be noted that the strength of conditioning is rather weak. There was no significant suppression of intake in animals exposed to flight. Rather, these animals failed to increase intake as was seen in animals from the Control group. Thus, a release from neophobia in Control animals with a failure to observe this release in Flight animals appears to create this difference.

The observed suppression of food intake could be a form of anorexia similar to that produced during prolonged exposure of animals to hyper-gravity during centrifugation, or to hypo-gravity during orbital flight. The coincident emergence of anorexia and CTA is consistent with the proposal that the rats became motion sick during the altered gravity during the brief exposures to parabolic flight. The magnitude of flight-induced anorexia is as great as, or greater than that produced by a form of passive, cross-coupled stimulation that is very provocative for humans. A) Anorexia following parabolic flight was present for 48 h while that produced by rotation was absent after only 24 h.

Informal observations regarding anorexia were conducted in both cats and squirrel monkeys to begin examination of this effect in animals with a complete emetic reflex. Both cats and squirrel monkeys were repeatedly observed to eat the food normally contained in their diets (cat food and bananas respectively) within a few minutes (e.g., less than 5 min) after vomiting. These observations indicate that anorexia is not necessarily present when the universally accepted indicator of motion sickness occurs. These effects have not been satisfactorily resolved as not formal experiments were conducted to test this issue further.

## **B. Effective Stimulus Parameters**

The specific parameters of stimulation that effectively produce motion sickness in animal

models was examined in several experiments. Two general results were documented with these experiments: (a) motion sickness can be produced in rodents, cats, and squirrel monkeys with moderate stimulation that is comparable to that which elicits sickness in humans; (b) stimuli that are very provocative for one species may be quite ineffective for producing sickness in another species.

Conditioned aversion can be produced in rodents with rotational stimulation that is of the magnitude that produces vomiting in squirrel monkeys, chimpanzees, and humans (Fox & Daunton (1982); Fox *et al.*, 1984). Further, this same stimulation can produce CTA in both cats and squirrel monkeys (Fox *et al.*, 1990). Thus, it is clear that conditioned aversions do not depend on severe motion challenges.

Detailed examination of eliciting stimuli in squirrel monkeys reflected that exposure to stimuli of increasing intensity to humans also elicited more severe sickness in the monkey (Fox *et al.*, 1982). An important result in this study, however, was the finding that stimuli that are extremely provocative for humans are effective for the squirrel monkey only when there is a requirement for the animal to maintain posture. When animals were exposed to provocative stimuli (cross-coupled stimulation) while movement was restricted at both the neck and waist, the same stimulus that elicited sickness with waist restraint only no longer was effective. Thus, it appears that a requirement for postural control during passive motion is necessary if motion sickness is to be elicited.

Examination of the role of vision in motion sickness produced the first demonstration of vomiting in cats and squirrel monkeys by visual stimulation alone (Daunton *et al.*, 1985). Sickness induced by visual stimulation alone is known in man and is very disruptive in certain instances (e.g., "simulator sickness"), but this has not been shown previously in an animal model. With regard to the problem of prediction, it was shown in this research that animals more prone to sickness by passive, whole-body stimulation also were more likely to become sick by optokinetic stimulation alone.

## **C. Neuroanatomy and Physiology**

### **1. Vasopressin.**

Vasopressin (AVP) is elevated in humans during reports of nausea and following vomiting (see Fox, 1992 for a review). Plasma AVP is dramatically elevated in cats following vomiting but the resting level of AVP in blood plasma

does not differ among cats that are selected to be highly susceptible or very resistant to linear acceleration. On the other hand, AVP in cerebrospinal fluid (CSF) is not elevated following motion sickness, but resting levels of AVP in CSF are lower in animals that vomited during motion than in those animals which did not vomit (Fox *et al.*, 1987). The precise mechanism for the release of AVP during motion sickness could not be determined. Systemic injection of AVP at dosages calculated to produce levels equivalent to those observed following vomiting failed to produce vomiting or to influence the onset of vomiting in cats that were susceptible or resistant to linear acceleration (Unpublished Data).

## **2. Area Postrema.**

Experiments using the lesion technique to examine the role of the area postrema showed that: (a) The area postrema is not involved in CTA that is produced by motion in rats (Sutton *et al.*, 1988); (b) Neither CTA nor vomiting are crucially dependent on the area postrema in either cats or squirrel monkeys (Fox, Corcoran & Brizzee, 1990). In combination with work by Borison and Borison (1986), these findings contributed to a reevaluation of the role of the area postrema in vomiting induced by motion (Daunton *et al.*, 1987). Several authors have now proposed theories which include several additional brainstem and/or circumventricular structures in the emetic response (see Fox, 1992 for references).

## **3. Vagus Nerve.**

A possible role for the vagus nerve in responses to motion is implied by results showing that the vagus nerve is crucial to CTA induced in rodents by exposure to motion (Fox & McKenna, 1988). Combined with other research, this finding shows that both vestibular and gastric neural systems contribute to the formation of CTA when motion is the stimulus. The specific mechanism by which gastric circuitry functions is unknown (Fox, Sutton, & McKenna, 1988), but we did provide evidence indicating that gastric afferents of the rat remain active for an extended period following brief physiological stimulation (Nijima *et al.*, 1987; 1988).

## **4. Immunocytochemistry.**

Preliminary evidence indicating a role for the vagus nerve either in motion sickness or in adaptation to stimuli producing motion sickness has been shown. Using immunocytochemistry we showed that the distribution pattern of

GABAergic terminals in the area postrema, nucleus tractus solitarius, area sub-postrema, and gelatinous nucleus closely resembles that of vagal afferent projections (D'Amelio *et al.*, 1988). In addition, the depletion of GAD immunoreactive in these areas after electrical stimulation of the vagus nerve seems to confirm that at least part of the GABAergic activity shown here corresponds with vagal afferents. The additional demonstration of substance P immunoreactivity in this study implies there may be important neuromodulatory functions mediated by neuropeptides.

## **D. Species Differences**

While conducting the studies discussed above to evaluate behavioral measures of and effective stimuli for motion sickness it became increasingly obvious that stimuli that elicited sickness and the syndromes observed in different species varied greatly. For example, linear acceleration, particularly earth-vertical acceleration, is an especially effective stimulus for eliciting motion sickness in cats while vertical axis rotation is remarkably noneffective. On the other hand, vertical axis rotation is very provocative for the squirrel monkey while linear acceleration has only minimal effectiveness with this species.

Species differences can occur in rather closely related species where similar reactions to stimuli might be expected. For example, although vertical axis rotation is very provocative for squirrel monkeys, we were unable to make rhesus monkeys motion sick with this stimulus (Corcoran, Fox, & Daunton, 1990). In fact, both anecdotal and experimental evidence indicate that the rhesus monkey is highly resistant to motion sickness. Workers in the Russian space program have reported "space sickness" but there have been no well controlled studies reporting on these effects (see Daunton, 1990 for a review of these points).

Differences of this type complicate the selection of appropriate animal models for studying the emetic reflex in general and motion sickness or the space adaptation syndrome in particular. Animal models will be crucial to the discovery and understanding of neurophysiological mechanisms of these phenomena, but considerable research will be required before answers come forth.

### III. CONCLUSIONS

All of the behavioral responses that have been examined as measures of motion sickness in animals are less than ideal. The only response that is universally accepted as a valid measure is vomiting. On initial consideration this appears to be a serious weakness in this area of research. However, it should be recognized that no other measures have been universally accepted for the assessment of motion sickness in humans. The most commonly used additional measure in human studies is nausea, but the assessment of nausea, even in humans can be quite inaccurate. Furthermore, there are no recognized physiological correlates of nausea in humans, further complicating the assessment of this response in animals.

The issue of prediction of susceptibility to motion sickness also is difficult. Significant attention has been directed to the problem of prediction in humans with only minimal success. While we found some evidence for predictive value in the level of AVP in CSF, this effect was not highly predictive and significant work would be required to understand this relationship adequately. As is the case in humans, plasma AVP was dramatically elevated in cats following vomiting, but there was no evidence in this research to indicate that the level of system AVP was predictive of susceptibility to motion sickness.

It is now abundantly clear that previous conceptions of the area postrema as a vomiting center in motion sickness were premature and incorrect. This conceptualization arose, in part, from over-interpretation of lesion experiments before many of the techniques of neuroscience that are in common use today were available. With present knowledge, many workers now propose by that the emetic reflex is mediated via circuitry in several circumventricular and brainstem regions. Important work remains to provide understanding of the specific neural mechanisms of the response that is so important in disease and travel by modern conveyances.

A general hypothesis that was developed during the course of this research project is that motion sickness is a phenomenon that may reflect only one of the outcomes of the more general effects of adaptation to unusual environmental conditions. Motion sickness arises when organisms are subjected to passive motion that results in atypical linear forces on the vestibular system. Passive motion of this type can elicit significant and pervasive adaptive responses in many systems other than the emetic reflex (e.g.,

motor coordination, postural reflexes, etc.). Consequently, it is reasonable to expect that many systems may be undergoing significant changes (i.e., adaptations) during periods when motion sickness occurs. In fact, one way to avoid motion sickness is to select a behavior that prevents adaptation of motor systems such as lying down or going to sleep. In this regard it should be noted that motion sickness occurred in squirrel monkeys only when there was a necessity to maintain posture. This hypothesis would suggest that motion sickness might simply be an unfortunate outcome of normal processes of adjusting the neuromuscular system to new, atypical environmental conditions. Although the specific mechanisms that may be involved in such processes are obscure at this time, discovery of the physiology and neural changes that underlie adaptation may predict the mechanisms that elicit motion sickness.



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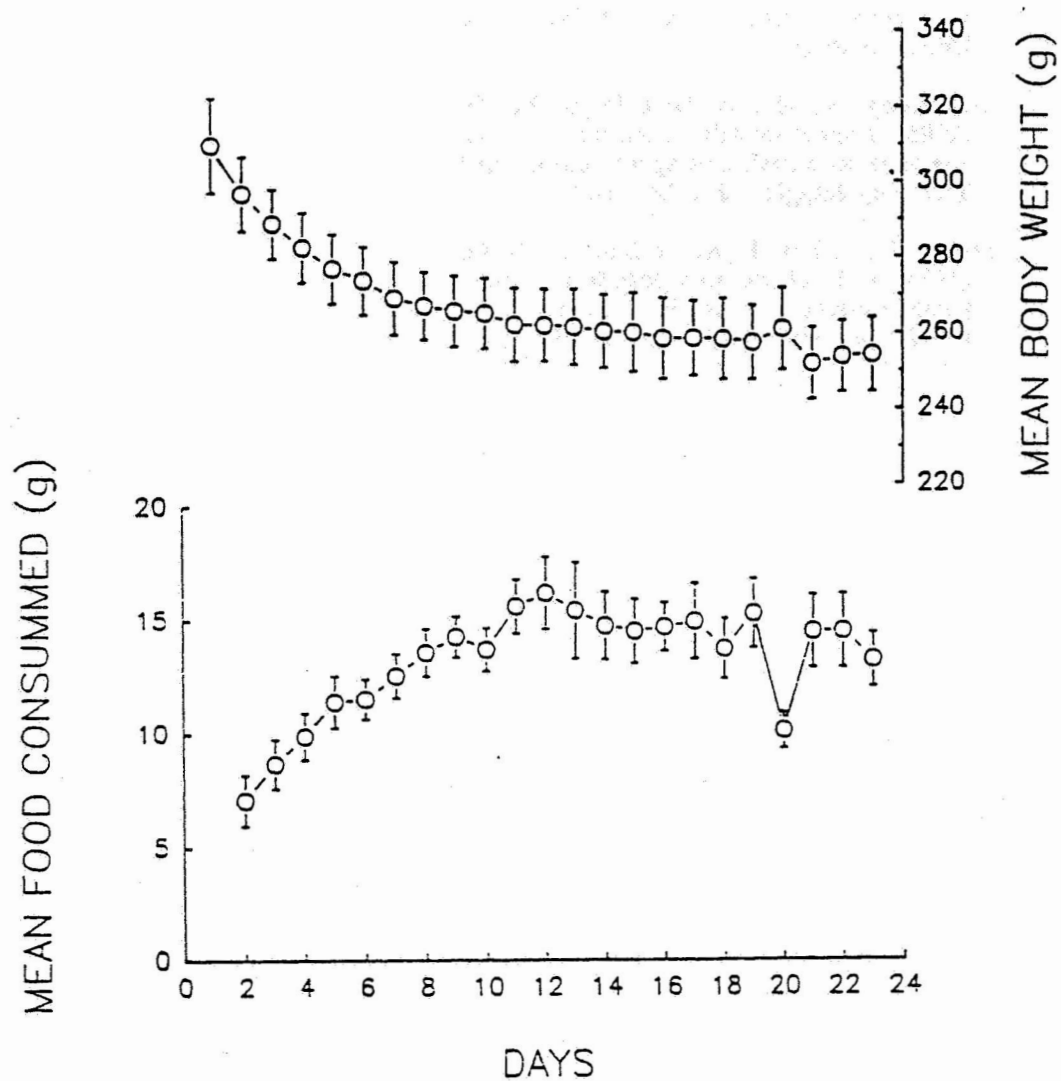


Figure 1. Mean Food Intake and Body Weight by Rats Exposed to Off-Vertical Rotation.

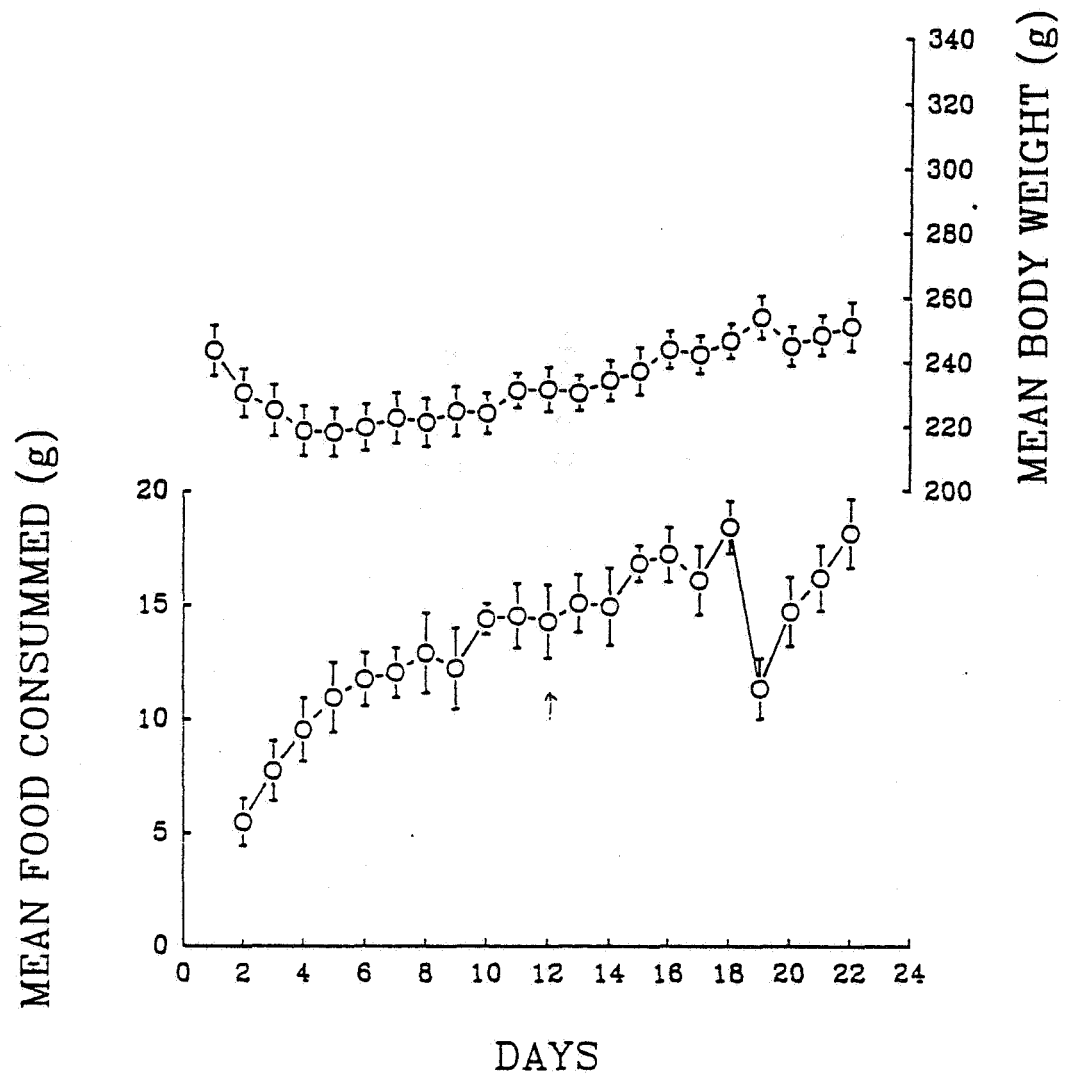


Figure 2. Mean Food Intake and Body Weight by Rats Exposed to Parabolic Flight.



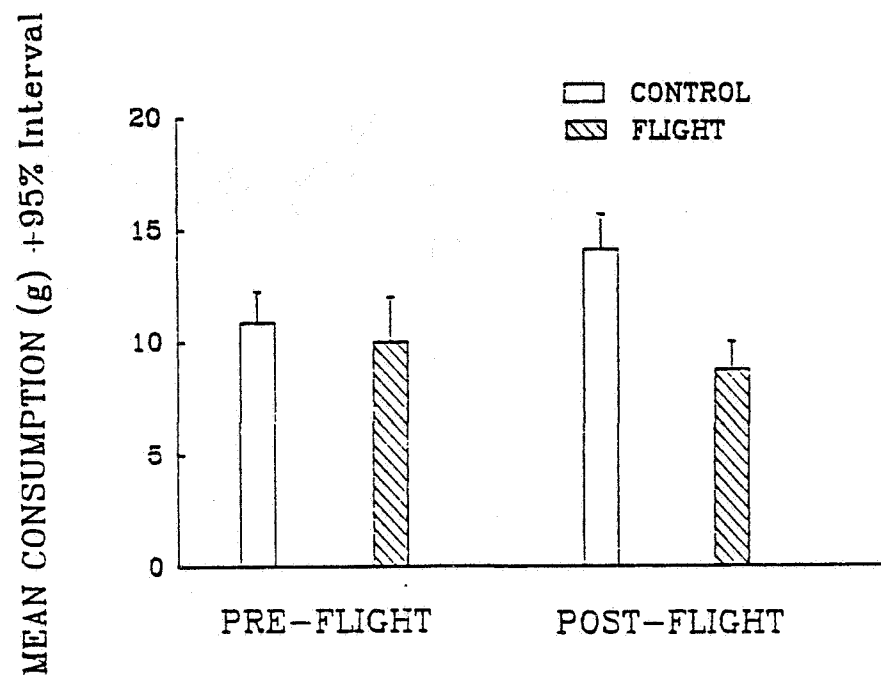


Figure 3. Mean Fluid Intake by Rats Prior to and Following Exposure to Parabolic Flight.

## VI. APPENDIX I.

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## VII. APPENDIX II.

### PAPERS at SCIENTIFIC MEETINGS

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- Diaz, L., Sutton, R., Graf, R., Wilright, S., & Fox, R. (1982). The magnitude of conditioned taste aversion depends upon preference for the averted flavor. Western Psychological Association, Sacramento, CA.
- Fox, R. A., Daunton, N. G., & Coleman, J. (1982). Susceptibility of the squirrel monkey to several different motion conditions. Minneapolis, MN (poster).
- Lauber, A. H., Kinnery, N. E., Fox, R. A., & Daunton, N. G. (1982). Flight-induced weightlessness produces conditioned taste aversion. Western Psychological Association, Sacramento, CA.
- Daunton, N., & Fox, R. A. (1983). Motion sickness elicited by passive rotation in squirrel monkeys: Modification by consistent and inconsistent visual stimulation at high and low frequencies. International Society of Posturography: 7th International Symposium, Houston, TX.
- Sutton, R. S., Fox, R. A., & Daunton, N. G. (1983). Relationship of area postrema to three putative measures of motion sickness in the rat. Boston, MA (poster).
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- Nagahara, A., Fox, R., Daunton, N. & Elfar, S. (1986). Detection of emetic activity in the cat by monitoring venous pressure and audio signals. Washington, DC (poster).
- D'Amelio, F., Daunton, N., & Fox, R. A. (1987). Immunocytochemical localization of glutamic acid decarboxylase (GAD) and Substance P in neural areas mediating motion-induced emesis. Effects of vagal stimulation on GAD immunoreactivity. International Symposium on Basic and Applied Aspects of Vestibular Function, University of Hong Kong, Hong Kong.
- Daunton, N., Brizzee, K., Corcoran, M., Crampton, G., D'Amelio, F., Elfar, S., & Fox, R. (1987). Reassessment of area



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Neuroscience Abstracts,  
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223.2 CHANGES IN PLASMA VASOPRESSIN DURING MOTION SICKNESS IN CATS. R. Fox\*, L. Keil, N. Daunton, D. Thomsen\*, M. Dictor\*, and O. Chee\*. NASA Ames Res. Center, Moffett Field, CA 94035 and San Jose State Univ., San Jose, CA 95192.

Changes in levels of plasma vasopressin (AVP) and cortisol (C) have been shown to be correlated with motion sickness and nausea in man. As part of the research aimed at validation of the cat as an appropriate animal model for motion sickness research, levels of these hormones were investigated in the cat during motion sickness elicited by vertical linear acceleration of approximately 0.6 Hz and  $1 \pm 0.6$  G.

In Study 1, 15 cats previously screened for susceptibility to motion sickness were prepared with indwelling jugular catheters to permit withdrawal of blood with minimal disruption of the stimulus and minimum stress to the animal. AVP and C were measured in blood samples obtained during exposure to vertical linear acceleration and during control sessions in which the animals were placed in the stationary apparatus. Samples were drawn according to a predetermined time schedule as follows: 10 min and 1 min prior to motion; 1, 5, 10, and 20 min after start of motion. Total duration of exposure to motion was 20 min. The data from this study indicate that both AVP and C are elevated during exposure to motion if emesis occurs. AVP reaches maximum levels during or about the same time as emesis, while C increases gradually throughout the period of vertical acceleration.

In Study 2, four cats were prepared with indwelling catheters and AVP was measured in blood withdrawn during exposure to the vertical linear acceleration. A single pre-motion sample was drawn 5 min prior to motion onset. Two series of samples consisting of three samples drawn at 3-min intervals were obtained during motion. The first series was initiated at emesis, and the second 25 min after emesis. Results show that levels of circulating AVP were elevated (2 to 27 times the control and pre-motion levels) in the samples taken during emesis and decreased, but remained 1 to 6 times above the pre-motion or control levels within 25 min.

The results of these two studies indicate that AVP is elevated during motion-produced emesis in the cat, and that AVP is more closely related to emesis than is C. These findings are in general agreement with those obtained from humans under motion sickness conditions, and indicate that it is appropriate to continue to use the cat in studies of hormone changes during motion sickness.